Should Psychiatrists Use Atypical Antipsychotics to Treat Nonpsychotic Anxiety?

by RONALD PIES, MD

Professor of Psychiatry, SUNY Upstate Medical University, Syracuse, New York; and Clinical Professor of Psychiatry, Tufts University School of Medicine, Boston, Massachussetts

Psychiatry (Edgemont) 2009;6(6):29–37

ABSTRACT

There is neurobiologically based, theoretical support for the use of antipsychotic medications in the treatment of anxiety, and two first-generation neuroleptics are approved by the United States Food and Drug Administration for the treatment of nonpsychotic anxiety. However, neuroleptics are associated with a large side effect burden, which has limited their utility in the treatment of nonpsychotic disorders. Because of their somewhat improved safety profile, atypical antipsychotics are increasingly used for the treatment of nonpsychotic anxiety. The published literature describing the efficacy of atypical antipsychotics in randomized, controlled trials involving patients with anxiety disorders is briefly reviewed, and the safety of atypical antipsychotics in nonpsychotic disorders is discussed. There is moderately strong controlled evidence supporting the use of some atypical antipsychotics, either as adjunctive treatment or monotherapy, in the treatment of nonpsychotic anxiety; however, the side effect burden of some atypical antipsychotics probably outweighs their benefits for most patients with anxiety disorders. The evidence to date does not warrant the use of atypical antipsychotics as first-line monotherapy or as first- or second-

FINANCIAL DISCLOSURES: Dr. Pies reports no relevant conflicts of interest or commercial ties with respect to this material.

ADDRESS CORRESPONDENCE TO: Dr. Ronald Pies, Box 332, Bedford MA 01730; E-mail: ronpies@massmed.org

KEY WORDS: atypical antipsychotic, anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, social anxiety disorder, off label, tardive dyskinesia, neuroleptic malignant syndrome, extrapyramidal side effects

line adjunctive therapy in the treatment of anxiety disorders. Rigorous, independently funded, long-term studies are needed to support the off-label use of atypical antipsychotics in the treatment of anxiety disorders. Nevertheless, some patients with highly refractory anxiety disorders may benefit from the judicious and carefully monitored use of adjunctive atypical antipsychotics. A careful risk-benefit assessment must be undertaken by the physician, on a case-by-case basis, with appropriate informed consent.

INTRODUCTION

Consider the case of Ms. B, a 37-year-old mother of two with a 20-year history of severe generalized anxiety disorder (GAD) diagnosed by current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria. She saw four different psychotherapists since her condition began and received both cognitive-behavioral and psychodynamically oriented psychotherapy. In addition, Ms. B was prescribed adequate courses of three different benzodiazepines, two tricyclic antidepressants, and three selective serotonin reuptake inhibitors (SSRIs) over the past decade. The most effective pharmacologic treatment in Ms. B's history was a very brief course of thioridazine (50mg/day) in the late 1980s, which was discontinued owing to complaints of dry mouth, constipation, and severe dizziness. Although she experienced modest improvement on a number of the other medication regimens, Ms. B remained "…wound up all the time, like my muscles are in knots…" and experienced restlessness, fatigue, difficulty concentrating, irritability, and difficulty falling asleep. Ms. B added, "I know it's neurotic, but I'm always waiting for the next shoe to drop—like something bad is going to happen to me or the kids, even though life is great." There was no evidence of a frank psychotic or delusional disorder, and Ms. B did not fit DSM-IV criteria for dysthymia or major depression. All laboratory and medical investigations turned up no abnormalities, and there was no history of drug or alcohol misuse. Ms. B said she "…saw on the internet that these new atypicals" were useful for anxiety and wanted to know if she could begin taking one.

Is it reasonable to try one of the atypical antipsychotics for a patient like Ms. B? What theoretical and empirical justification is there for using an antipsychotic for a nonpsychotic condition? What do the controlled data show, with respect to the efficacy of atypical antipsychotics (AAPs) for anxiety disorders, either as adjunctive treatment or monotherapy? What are the medical risks of using AAPs off label in such cases? These questions are the focus of the present commentary.

This article is not a comprehensive review of pharmacologic or nonpharmacologic treatment of anxiety; rather, it represents the author's synthesis and recommendations regarding the use of AAPs for specific anxiety disorders. For a more fine-grained analysis of the research data, two recent comprehensive reviews are referenced.[1,2]

HISTORICAL PERSPECTIVE

Recently graduated residents in psychiatry may not be aware that two pharmacologic "dinosaurs"—both conventional neuroleptics—have US Food and Drug Administration (FDA)-approved labeling for the treatment of anxiety. Trifluoperazine is approved for short-term treatment of generalized, nonpsychotic anxiety, though not as "initial therapy;" and perphenazine (in combination with the tricyclic antidepressant amitriptyline Triavil) is approved for "treatment of depression and anxiety." Though a review of "typical" antipsychotics (neuroleptics) is beyond the scope of this commentary, it is noteworthy that 15 years elapsed between the landmark 1986 study by Mendels et al of trifluoperazine[3] and the FDA-approved labeling of this agent for short-term treatment of GAD in 2001.[2] One wonders whether this reflected some ambivalence on the part of the FDA reviewers, but this author was unable to discover any explanation for the delay (K. Gao MD, personal communication, 3/09/09).

The Mendels study was a large (n=415), randomized, double-blind, placebo-controlled trial of trifluoperazine (2–6mg/day). The active drug was superior to placebo on all outcome measures, including the Hamilton Anxiety Scale. The Mendels study avoided many methodological problems with similar studies done in the early 1980s[2] and encouraged the view that at least some antipsychotics have significant anxiolytic properties. However, the Mendels study followed patients for only four weeks; and, to this day, there are few, if any, long-term safety data on the use of standard neuroleptics as anxiolytics. Indeed, the FDA's own caveats for trifluoperazine suggested potential problems with long-term use of typical antipsychotics as anxiolytics. The labeling information states that "Stelazine is not the first drug to be used in therapy for most patients with nonpsychotic anxiety because certain risks associated with its use are not shared by common alternative treatments (i.e., benzodiazepines)."[4]

As we shall see, these risks are not necessarily eliminated when AAPs are considered (see "Medical Risks"). Indeed, despite encouraging—but as yet unpublished[5–8]—controlled data supporting the use of quetiapine for nonpsychotic anxiety, no AAP has FDA-approved labeling for any anxiety disorder, as of this writing. In April 2009, the FDA Psychopharmacologic Drugs Advisory Committee (PDAC) conducted a review of supplemental new drug applications (sNDAs) for AstraZeneca's Seroquel XR (quetiapine fumarate extended-release tablets). The sNDAs were proposed for the treatment of major depressive disorder (MDD) and GAD. Essentially, the PDAC concluded that Seroquel XR was effective in MDD as both monotherapy and adjunctive therapy; and also effective in GAD as monotherapy. But whereas the PDAC

found the drug acceptably safe as an adjunctive treatment for MDD, the committee did not find Seroquel XR acceptably safe as monotherapy for "broad treatment" of MDD, nor acceptably safe as monotherapy for the treatment of GAD. While a detailed discussion of the PDAC's deliberations are beyond the scope of this review, specific concerns as to the safety of Seroquel XR in GAD may be found at: http://www.fda.gov/ohrms/dockets/ac/09/transcripts/2009-4424t2-part1.pdf

THEORETICAL FOUNDATION FOR AAP USE IN NONPSYCHOTIC ANXIETY

Anxiety is a complex human phenomenon, with multiple biological, psychological, and sociocultural components. From a medical standpoint, the complexity of anxiety is aptly summarized by Tefera and Tomao,[9] as such:

"Anxiety is a complex feeling of apprehension, fear, and worry often accompanied by pulmonary, cardiac, and other physical sensations. It is a common condition that can be a self-limited physiologic response to a stressor, or it can persist and result in debilitating emotions. When pathologic, it can exist as a primary disorder, or it can be associated with a medical illness or other primary psychiatric illnesses (e.g., depression, psychosis)."

It would be naïve to suggest that we fully understand the pathophysiology of severe anxiety states, much less that all the DSM-IV anxiety disorders arise from the same biochemical aberration or abnormality. The neurobiological basis of anxiety is comprehensively reviewed by Charney and Drevets.[10]

Notwithstanding anxiety's diverse origins, there appears to be pathophysiological derangements that accompany many types of severe anxiety and which bear on the relevance of AAPs as anxiolytics. Thus, there is ample evidence that aberrant γ-aminobutyric-acid (GABA) circuits are integrally involved in anxiety disorders.[11] In crude terms, there appears to be reduced GABAergic function in some severe anxiety states. But the situation is far more complex. For example, as Charney and Drevets[10] show, neuropeptide Y, substance P, the monoaminergic neurotransmitters (norepinephrine, serotonin, dopamine), and glutamate are almost certainly involved in the pathophysiology of anxiety. Most likely, there are important differences among the various anxiety disorders with respect to the relative contributions of these neurochemicals. For example, there is little evidence that dopaminergic dysfunction plays a primary role in most anxiety disorders, including panic disorder.[10] However, there is some evidence of reduced dopamine-receptor binding in social phobia.[12] And in combat-related posttraumatic stress disorder (PTSD), there is preliminary evidence that susceptibility is associated with a polymorphism in the DRD2 gene—the gene that encodes the D2 type of dopamine receptor.[13]

In any case, because the AAPs have very broad pharmacodynamic effects, there are many ways in which the AAPs could influence anxiety—and not necessarily or reliably in a favorable direction. Thus, AAPs appear to have complex and perhaps regionally specific effects on GABA in the brain, based on *in-vitro* and animal models. For example, clozapine appears to antagonize $GABA_A$ receptors in cultured neurons,[14] which would not point to anxiolytic properties, all other things being equal. On the other hand, some evidence suggests that olanzapine counteracts stress-induced, anxiety-like behavior in rats[15] via an indirect effect on the GABAergic system. This seems to be mediated by olanzapine's effects on allopregnanolone, a neuroactive steroid that activates the GABAA receptor complex.

The AAPs have complex effects on dopamine and dopamine receptors, depending on the specific drug. Thus, risperidone binds "tightly" and chronically to D2 receptors, whereas quetiapine and olanzapine appear to have a "fast-off" action at D2 receptors, thus mitigating their D2 antagonism.[16] This may partly account for the reduced likelihood of extrapyramidal side effects and akathisia with quetiapine or olanzapine use, compared with risperidone or conventional neuroleptics—though these findings are variable and dose related. As we shall see, akathisia may be a cause of severe anxiety or agitation. Finally, the AAPs also have histamine receptor antagonist properties to varying degrees, and both animal and human data suggest that the histaminergic system is implicated in anxiety states.[17]

Aripiprazole is unusual among the AAPs in having partial agonism at the D2 receptor, suggesting that its effects may vary with ambient dopamine levels. Aripiprazole shares with the other AAPs antagonist effects at the serotonin 2A ($5\text{-}HT_{2A}$) receptor; however, aripiprazole also has partial agonist activity at the 5-HT1A receptor,[18] which is known to be involved in anxiolysis. For example, the approved anxiolytic buspirone probably exerts some of its effects by acting as a $5\text{-}HT_{1A}$ partial agonist.[19]

What is the upshot of all these complex neurochemical nuances? In the author's view, the possible interactions between AAPs and the neurochemicals that mediate anxiety are too complex to predict the effect of AAPs on anxiety. It is even more hazardous to predict an AAP's effect on any given anxiety disorder, since the pathophysiology probably varies among these disorders. There is also no reason to assume that the AAPs have consistent "class effects" on anxiety, as each agent has a distinct pharmacodynamic profile. Thus, we will need empirical investigations of specific AAPs in specific anxiety disorders to learn which agents are useful in treating which disorders. That said, there are theoretical reasons to hypothesize that some AAPs may have beneficial effects on some types of anxiety, with the caveat that AAPs might actually worsen anxiety in some cases—for example, by inducing akathisia.

SYNOPSIS OF PUBLISHED CONTROLLED STUDIES OF AAPS IN ANXIETY DISORDERS

Investigations of AAPs as anxiolytics consist mainly of adjunctive therapy studies, with only a few studies of AAP monotherapy. This commentary will focus on randomized, double-blind, placebo-controlled trials [RCTs] of specific anxiety disorders—not on anxiety as a symptom in the context of other diagnoses. Since most data are derived from studies of GAD, refractory obsessive-compulsive disorder (OCD), PTSD, and social anxiety disorder (SAD), we will focus on published studies of these conditions. More detailed reviews are provided by Bandelow et al [1] and Gao et al.[2] Nonpublished presentations or abstracts are also briefly discussed.

The general findings of the present review are summarized in Table 1. Many of these studies have small sample sizes (n=7–70) and must therefore be considered preliminary findings. Since there are no "head-to-head" comparisons of AAPs, it is also premature to conclude that any particular AAP is a "drug of choice" for the adjunctive treatment of anxiety disorders. In gross numerical terms—and with the caveat that we are lumping together heterogeneous studies—the number of studies favoring drug over placebo is as follows: quetiapine, 2 of 5; olanzapine, 4 of 6; and risperidone, 8 of 10. While this tally might suggest that risperidone has more robust anxiolytic effects than the other agents studied, RCTs using a head-to-head design are needed to confirm this preliminary impression. Moreover, risperidone may be less useful in GAD than in either refractory OCD or PTSD. To the author's knowledge, there are no published RCTs using aripiprazole or ziprasidone in specific anxiety disorders, though aripiprazole appears to be effective adjunctively in patients with major depression presenting with anxious features.[20]

MEDICAL RISKS OF USING AAPS OFF LABEL FOR ANXIETY

In recent years, several reports have emerged involving pharmaceutical company promotion of unsupported off-label use of AAPs and other psychotropics.[42] This is troubling from a clinical, ethical, and legal perspective. While there is nothing wrong with judicious off-label prescribing under certain carefully defined conditions, the use of AAPs for anxiety disorders raises a number of concerns. First, as the foregoing review suggests, there are only preliminary published data supporting the use of AAPs in anxiety disorders. Of the RCTs reviewed, one third (7 of 21) yielded no significant benefit of the AAP compared with placebo. It should be noted that in data from several randomized, controlled—but unpubished—studies submitted to the FDA (see http://www.fda.gov/ohrms/dockets/AC/09/briefing/2009-4424b2-03-AstraZeneca.pdf) quetiapine fumarate extended-release tablets showed similar efficacy (i.e., small to moderate effect size) compared with other anxiolytic agents (personal communication, K. Gao MD, 5/15/09); quetiapine also appeared generally well-tolerated. Nevertheless, there are substantial medical risks associated with the use of antipsychotic medications, including the so-called atypical agents. (Some clinicians, noting more pharmacodynamic similarities than differences between older neuroleptics and AAPs, have urged the abandonment of the term *atypical antipsychotic*.) Some of these risks are also associated with substantial medicolegal liability.

Posternak has recently reviewed the medical risks associated with AAPs.[43] Contrary to the impression of some clinicians, AAPs have not eliminated serious risks commonly associated with older neuroleptics, including tardive dyskinesia (TD) and neuroleptic malignant syndrome (NMS). Although TD rates are lower with AAPs than with most first-generation neuroleptics—the annual incidence rates in adults are roughly 0.8% and 5.4%, respectively—a psychiatrist treating 100 patients with AAPs could still expect to see one case of AAP-related TD per year—and rates are likely higher in elderly patients.[43,44]

Most data showing AAP-associated extrapyramidal side effects (EPS) and TD rates are derived from patients with schizophrenia. There is no reason to assume that these relatively low rates will hold true for patients with anxiety (or affective) disorders. Recently, for example, Gao et al found that patients with bipolar depression are more vulnerable to acute EPS than those with bipolar mania or schizophrenia during antipsychotic treatments.[45]

Equally worrisome, and much more common than TD or NMS, are metabolic complications associated with the AAPs, such as weight gain or glycemic and lipid abnormalities.[46] Metabolic syndrome (usually defined in terms of weight gain, hypertension, fasting hyperglycemia, and dyslipidemia) may occur in as many as 25 percent of patients treated with olanzapine or risperidone, depending on criteria used.[47] Distinctions among the AAPs should be noted, however. For example, Newcomer's review[46] concluded that "…clozapine and olanzapine treatment are associated with the greatest risk of clinically significant weight gain," whereas there is "…no evidence at this time to suggest that ziprasidone and aripiprazole treatment are associated with an increase in risk for diabetes, dyslipidemia or other adverse effects on glucose or lipid metabolism." It appears likely that risperidone and quetiapine pose an intermediate level of overall metabolic risk,[46] but there is a paucity of prospective, head-to-head (comparative) data on this point. Recently, the cardiac side effects of the AAPs have been described, including increased risk of arrhythmia and sudden cardiac death; however, this risk is apparently at least as high with older neuroleptics.[43,48] The tendency of most AAPs to increase the QTc interval—albeit in a small proportion of patients[49]—may be clinically significant in a subgroup of patients with pre-existing long QTc, or those taking concomitant drugs that inhibit metabolism of the AAP. Finally, the risk of medication abuse

TABLE 1. Published randomized, double-blind, placebo-controlled trials of AAPs for anxiety disorders

DISORDER	STUDY	AAP STUDIED	AGENTS AUGMENTED/ BRIEF STUDY DESCRIPTION	OUTCOME ON PRIMARY MEASURE	COMMENTS
GAD	Simon et al[21]	Quetiapine	Quetiapine versus PBO augmentation for individuals with GAD remaining symptomatic with initial paroxetine CR pharmacotherapy	QUET = PBO on HAM-A	Small sample size (N=22)
	Merideth et al[22]	Quetiapine	Once-daily quetiapine extended-release monotherapy vs. PBO or escitalopram in acute treatment of GAD	QUET > PBO on HAM-A (escitalopram also > PBO)	Large (n=854) multicenter study
	Pollack et al[23]	Quetiapine	Augmentation with olanzapine or PBO for patients remaining symptomatic on fluoxetine	OLZ > PBO on HAM-A	Significant weight gain in OLZ group
	Brawman-Mintzer et al[24]	Risperidone	Patients with refractory GAD, despite anxiolytic for at least 4 weeks, received adjunctive treatment with PBO or low dose RSP	RSP > PBO on HAM-A	No significant differences (RSP vs. PBO) on some secondary measures, including CGI-S; RSP generally well tolerated
	Pandina et al[25]	Risperidone	GAD patients with CGI-S rating of 4 or more, despite at least 8 weeks of anxiolytic, randomized to adjunctive RSP or PBO	RSP = PBO on PaRTS-A	PaRTS-A is newly validated instrument that measures symptoms most troublesome to individual patients; study had very high PBO response rate.
	Sheehan et al[26]	Risperidone	Anxiolytic effect of risperidone monotherapy vs. PBO evaluated in patients with bipolar disorder and a co-occurring GAD or panic disorder	RSP = PBO on CGI-21 Anxiety	RSP-treated group had more patients with mixed states and lifetime panic disorder at randomization than PBO group; RSP worsened anxiety in subgroup of patients with panic disorder
ROCD	Shapira et al[27]	Olanzapine	PBO-controlled addition of olanzapine to fluoxetine in OCD subjects who were partial or nonresponders to open-label fluoxetine trial	OLZ = PBO on YBOCS	N/A
	Bystritsky et al[28]	Olanzapine	Olanzapine or PBO added to fluoxetine, paroxetine, or clomipramine in SRI nonresponders	OLZ > PBO on YBOCS	Small sample size (n=26); no significant difference on HAM-A; OLZ generally well tolerated
	Denys et al[29]	Olanzapine	Quetiapine added to SRI in patients unresponsive to at least twp different SRIs at maximum tolerated dose	QUET > PBO on YBOCS	somnolence, dry mouth, weight gain, and dizziness reported with quetiapine
	Carey et al[30]	Olanzapine	Quetiapine augmentation in subjects who had responded inadequately to open-label treatment with an SRI	QUET = PBO on YBOCS	N/A
	McDougle et al[31]	Risperidone	Patients refractory to SRI randomized to six weeks of risperidone or PBO; PBO-treated patients subsequently received identical open-label trial of risperidone addition	RSP > PBO on YBOCS	Risperidone addition superior to PBO in reducing depressive and anxiety symptoms; mild, transient sedation with RSP; OCD patients with and without comorbid chronic tic disorders or schizotypal personality disorder responded

TABLE 1, CONTINUED. Published randomized, double-blind, placebo-controlled trials of AAPs for anxiety disorders

DISORDER	STUDY	AAP STUDIED	AGENTS AUGMENTED/ BRIEF STUDY DESCRIPTION	OUTCOME ON PRIMARY MEASURE	COMMENTS
ROCD, continued	Hollander et al[32]	Risperidone	Augmentation with 8 weeks of either risperidone or PBO (n=6) following at least 12 weeks of SRI treatment (failure of at least two SRI trials)	RSP > PBO on YBOCS	Small sample size (n=16)
	Li et al[33]	Risperidone Haloperidol	Crossover study comparing benefits of two-week adjunctive treatment with risperidone, haloperidol, or PBO in patients with continued severe OCD symptoms despite stable dose of SRI (>12 wk)	RSP, haloperidol each > PBO on YBOCS	Active drug effect significant for obsessions, with trend for effect on compulsions. RSP but not haloperidol also improved depressed mood
	Erzegovesi et al[34]	Risperidone	Evaluated efficacy of risperidone vs. PBO addition in fluvoxamine-refractory patients; also investigated whether RSP could boost efficacy of fluvoxamine in fluvoxamine responders	RSP > PBO on YBOCS	Significant effect of RSP addition at end of double-blind phase (18th week) only for fluvoxamine-refractory patients
PTSD	Butterfield et al[35]	Olanzapine	Ten-week evaluation in which patients were randomized 2:1 to either olanzapine or PBO	OLZ = PBO on SIP, TOP-8	High PBO response rate, small sample size (n=15)
	Stein et al[36]	Olanzapine	Adjunctive olanzapine or PBO for SSRI-resistant combat-related PTSD patients minimally responsive to SRI at maximum tolerated dose	OLZ > PBO on CAPS	OLZ augmentation = significantly greater reduction than PBO in specific measures of PTSD, depressive, and sleep disorder symptoms; clinician-rated global response rates not significantly different OLZ vs. PBO
	Hamner et al[37]	Risperidone	Examined efficacy of risperidone for psychotic symptoms in combat veterans with chronic PTSD and comorbid psychotic features	RSP > PBO on PANSS	CAPS ratings (for PTSD) did not differ significantly between RSP, PBO groups, but RSP > PBO for "re-experiencing" subscale at Week 5
	Bartzokis et al[38]	Risperidone	Adjunctive risperidone in treatment of chronic combat-related PTSD (RSP added in most cases to antidepressants anxiolytics, or hypnotics)	RSP > PBO on CAPS	Significantly greater improvement observed in subjects receiving RSP compared to PBO on CAPS-total and CAPS-D (arousal) subscale scores, and on HAM-A, PANSS-P
	Padala et al[39]	Risperidone	After washout from other psychotropic medications, RSP monotherapy for PTSD related to sexual assault and domestic abuse in women	RSP > PBO on TOP-8	Similar results on CAPS, HAM-A, HAM-D
SAD	Barnett et al[40]	Olanzapine	Evaluation of olanzapine monotherapy	OLZ > PBO on BSPS and SPIN	Small sample size (n=12: 7 OLZ and 5 PBO); OLZ and PBO both associated with negligible weight gain
	Vaishnavi et al[41]	Quetiapine	Evaluation of quetiapine monotherapy	QUET = PBO on BSPS, CGI	Quetiapine showed a large effect size on the SPIN (a secondary measure)

Abbreviation Key: BSPS = Brief Social Phobia Scale; CAPS = Clinician Administered PTSD Scale; CGI = Clinical Global Impression; GAD = generalized anxiety disorder; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; OCD = obsessive-compulsive disorder; OLZ = olanzapine; PANSS = Positive and Negative Syndrome Scale; PaRTS-A = Patient-Rated Troubling Symptoms Scale for Anxiety; PBO = placebo; PTSD = posttraumatic stress disorder; QUET = quetiapine; ROCD = refractory obsessive compulsive disorder; RSP = risperidone; SAD = social anxiety disorder; SIP = Structured Interview for PTSD; SPIN = Social Phobia Inventory; SRI = serotonin reuptake inhibitor; TOP-8 = Treatment Outcome PTSD scale; YBOCS = Yale-Brown Obsessive Compulsive Scale; > = significantly superior to

and dependence, although rarely associated with antipsychotic medications, has become a concern with several AAPs, particularly olanzapine[50] and quetiapine.[51] Once again, prospective, head-to-head comparisons are needed to detect genuine differences in abuse liability among the AAPs.

In short, the medical risks of AAPs among patients with psychotic disorders are far from rare or trivial. We may not be able to infer rates of AAP side effects in patients with anxiety disorders based on such reports, but a conservative operating assumption would hold that comparable risks exist for patients with anxiety disorders.

CONCLUSIONS AND RECOMMENDATIONS

Based on a review of published RCTs, there is moderately strong evidence that several atypical antipsychotic agents may have significant anti-anxiety effects, when used as adjunctive treatment in some anxiety disorders. The evidence from published studies appears to be most robust for adjunctive risperidone in the treatment of refractory OCD and PTSD, but further RCTs using a head-to-head design are needed. If unpublished data on quetiapine fumarate are confirmed in independently funded RCTs, this agent could hold promise in the treatment of refractory GAD.

Nonetheless, in this reviewer's opinion, the evidence to date does not warrant the use of AAPs as monotherapy in the treatment of anxiety disorders. Neither do the studies reviewed support the use of AAPs as either first- or even second-line agents in the adjunctive treatment of anxiety disorders. There are, in the first place, many effective agents (including SSRIs, SNRIs, benzodiazepines, and buspirone) that already have FDA-approved labeling for the treatment of anxiety disorders and which have a more favorable risk-benefit ratio, compared with AAPs. The medical risks associated with AAPs may vary from agent to agent and disorder to disorder in unpredictable ways. For example, in the only study of bipolar disorder and co-occuring panic disorder or GAD, Sheehan et al[26] found not only that risperidone was not superior to placebo in reducing anxiety symptoms, but also that it actually worsened anxiety in some patients with panic disorder.

In the absence of frank psychotic symptoms, refractory anxiety disorders should be treated by means of drug substitution within a given class of agents, such as switching to a different SSRI or SNRI or with combinations of agents already approved for treatment of anxiety disorders, such as combined SSRI/benzodiazepine treatment. Forms of psychotherapy known to be effective in anxiety disorders—such as cognitive-behavioral therapy—should also be offered to the patient prior to considering an AAP.[1] In the author's opinion, AAPs should be reserved as "third-line" agents for patients who do not respond to already-approved anxiolytics and/or psychotherapy or who are poor candidates for approved and validated treatments. For example, Ms. B—who had poor results from adequate courses of three different benzodiazepines, two tricyclic antidepressants, and three SSRIs—would be an appropriate candidate for an AAP trial, assuming she had no medical contraindications. (An EKG to rule out a long QTc would probably be prudent). Other appropriate candidates for an AAP trial could include markedly anxious patients who refuse psychotherapy or who have relative contraindications to SSRIs, buspirone, or benzodiazpines (e.g., patients with histories of alcohol or other substance abuse would generally not be good candidates for benzodiazepine treatment.) The physician must weigh such factors on a case-by-case basis, calculating as carefully as possible the overall risk-benefit ratio of the proposed treatment.

Informed consent is particularly important when AAPs are prescribed off label, especially given rare but serious risks, such as NMS or TD. Medicolegal risks of such off-label prescribing should also be considered. More common problems, such as weight gain, metabolic dysfunction, and cardiac abnormalities, must be carefully considered, with appropriate clinical and laboratory monitoring for such effects. Nonetheless, with careful assessment, close monitoring, and appropriate informed consent, some patients with refractory anxiety disorders are likely to benefit from adjunctive treatment with AAPs.

ACKNOWLEDGMENTS

The author wishes to thank Dr. Keming Gao and Dr. David Osser for their helpful comments on earlier drafts of this manuscript and Ms. Chantelle Marshall for her assistance with editing. The views expressed here are solely those of the author.

REFERENCES

1. Bandelow B, Zohar J, Hollander E, et al. World Federation of Society of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—first revision. *World J Biol Psychiatry*. 2008;9:248–312.
2. Gao K, Muzina D, Gajwani P, Calabrese JR. Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: a review. *J Clin Psychiatry*. 2006;67:1327–1340.
3. Mendels J, Krajewski TF, Huffer V, et al. Effective short-term treatment of generalized anxiety disorder with trifluoperazine. *J Clin Psychiatry*. 1986;47:170–174.
4. Stelazine [package insert]. Collegeville, PA: GlaxoSmithKline; 2001. Available at: http://www.fda.gov/cder/foi/label/2001/11552s112lbl.PDF. Accessed April 14, 2009.
5. Brawman-Mintzer O, Nietert PJ, Rynn M, et al. Quetiapine monotherapy in patients with GAD. In the New Research Abstract of the 159th Annual Meeting of American Psychiatric Association, Toronto, Canada, May 20–25, 2006. NR: 634.

6. Chouinard G, Bandelow B, Ahokas A, et al. Once-daily extended release quetiapine fumarate (Quetiapine XR) monotherapy in generalized anxiety disorder: a phase III, double-blind, placebo-controlled study. In the Abstract Viewer of the 46th American College of Neuropsychopharmacology Annual Meeting, Boca Raton, Florida, USA. December 9–13, 2007:25.
7. Joyce M, Khan A, Atkinson S, et al. Efficacy and safety of extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalized anxiety disorder (GAD). In the New Research Abstract of the 159th Annual Meeting of American Psychiatric Association, Washington DC, USA, May 3–8, 2008. NR:3138.
8. Katzman M, Brawman-Mintzer O, Reyes E, et al. Extended release quetiapine fumarate (quetiapine XR) monotherapy in maintenance treatment of generalized anxiety disorder (GAD): efficacy and tolerability results from a randomized, placebo-controlled trial. In the New Research Abstract of the 159th Annual Meeting of American Psychiatric Association, Washington DC, USA, May 3–8, 2008. NR:3140.
9. Tefera L, Tomao LC. Anxiety. eMedicine Emergency Medicine. 2008 Nov 20. Available at: http://emedicine.medscape.com/article/805265-overview. Accessed April 14, 2009.
10. Charney DS, Drevets WC. Neurobiological basis of anxiety disorders. In: Davis KL, Charney D, Coyle JT, Nemeroff C (eds). *Neuropsychopharmacology: The Fifth Generation of Progress*. Philadelphia: Lippincott Williams & Wilkins; 2002:901–930.
11. Nemeroff CB. The Role of GABA in the pathophysiology and treatment of anxiety disorders. *Psychopharmacol Bull*. 2003;37:133–146.
12. Tiihonen J, Kuikka J, Bergström K, et al. Dopamine reuptake site densities in patients with social phobia. *Am J Psychiatry*. 1997;154:239–242.
13. Voisey J, Swagell CD, Hughes IP, et al. The DRD2 gene 957C>T polymorphism is associated with posttraumatic stress disorder in war veterans, compared with controls. *Depress Anxiety*. 2009;26:28–33.
14. Michel FJ, Trudeau LE. Clozapine inhibits synaptic transmission at GABAergic synapses established by ventral tegmental area neurones in culture. *Neuropharmacology*. 2000;39:1536–1543.
15. Locchi F, Dall'olio R, Gandolfi O, Rimondini R. Olanzapine counteracts stress-induced anxiety-like behavior in rats. *Neurosci Lett*. 2008;438:146–149.
16. Kapur S, Zipursky R, Jones C, et al. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry*. 2000;57:553–559.
17. Zarrindast MR, Valizadegan F, Rostami P, Rezayof A. Histaminergic system of the lateral septum in the modulation of anxiety-like behaviour in rats. *Eur J Pharmacol*. 2008;583:108–114.
18. Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, Yocca FD, Molinoff PB. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther*. 2002;302:381–389.
19. Eison AS, Eison MS. Serotonergic mechanisms in anxiety. *Prog Neuropsychopharmacol Biol Psychiatry*. 1994;18(1):47–62.
20. Trivedi MH, Thase ME, Fava M, et al. Adjunctive aripiprazole in major depressive disorder: analysis of efficacy and safety in patients with anxious and atypical features. *J Clin Psychiatry*. 2008;69:1928–1936.
21. Simon NM, Connor KM, LeBeau RT, et al. Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. *Psychopharmacology (Berl)*. 2008;197:675–681.
22. Merideth C, Cutler A, Neijber A, et al. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in the treatment of generalized anxiety disorder. *Eur Neuropsychopharmacol*. 2008;18:S499–S500.
23. Pollack MH, Simon NM, Zalta AK, et al. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. *Biol Psychiatry*. 2006;59:211–215.
24. Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2005;66:1321–1325.
25. Pandina GJ, Canuso CM, Turkoz I, et al. Adjunctive risperidone in the treatment of generalized anxiety disorder: a double-blind, prospective, placebo-controlled, randomized trial. *Psychopharmacol Bull*. 2007;40(3):41–57.
26. Sheehan DV, McElroy SL, Harnett-Sheehan K, et al. Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety. *J Affect Disorder*. In press.
27. Shapira NA, Ward HE, Mandoki M, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2004;55:553–555.
28. Bystritsky A, Ackerman DL, Rosen RM, et al. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry*. 2004;65:565–568.
29. Denys D, de Geus F, van Megen HJ, Westenberg HG. A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. *J Clin Psychiatry*. 2004;65:1040–1048.
30. Carey PD, Vythilingum B, Seedat S, et al. Quetiapine augmentation of SRIs in treatment refractory

obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study. *BMC Psychiatry*. 2005 Jan 24;5:5.
31. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:794–801.
32. Hollander E, Baldini Rossi N, Sood E, Pallanti S. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol*. 2003;6:397–401.
33. Li X, May RS, Tolbert LC, et al. Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study. *J Clin Psychiatry*. 2005;66:736–743.
34. Erzegovesi S, Guglielmo E, Siliprandi F, Bellodi L. Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Eur Neuropsychopharmacol*. 2005;15:69–74.
35. Butterfield MI, Becker ME, Connor KM, et al. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. *Int Clin Psychopharmacol*. 2001;16:197–203.
36. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002;159:1777–1779.
37. Hamner MB, Faldowski RA, Ulmer HG, et al. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. *Int Clin Psychopharmacol*. 2003;18:1–8.
38. Bartzokis G, Lu PH, Turner J, et al. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry*. 2005;57:474–479.
39. Padala PR, Madison J, Monnahan M, et al. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. *Int Clin Psychopharmacol*. 2006;21:275–280.
40. Barnett SD, Kramer ML, Casat CD, et al. Efficacy of olanzapine in social anxiety disorder: a pilot study. *J Psychopharmacol*. 2002;16:365–368.
41. Vaishnavi S, Alamy S, Zhang W, et al. Quetiapine as monotherapy for social anxiety disorder: a placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:1464–1469.
42. Waknine Y. Off-label use of atypical antipsychotics linked to increased mortality in elderly. Medscape Alert. 2005 April 12. Available at: http://www.medscape.com/viewarticle/502902. Accessed April 14, 2009.
43. Posternak M. Prescribing atypical antipsychotics: what are the risks? *The Carlat Psychiatry Report*. 2009;7:3–8.
44. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry*. 2004;161:414–425.
45. Gao K, Kemp DE, Ganocy SJ, et al. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *J Clin Psychopharmacol*. 2008;28:203–209.
46. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19 Suppl 1:1–93.
47. Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia—a randomized double-blind controlled, short-term prospective study. *Schizophr Res*. 2008;101(1-3):266–272.
48. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;36:225–235.
49. Mackin P, Young AH. QTc interval measurement and metabolic parameters in psychiatric patients taking typical or atypical antipsychotic drugs: a preliminary study. *J Clin Psychiatry*. 2005;66:1386–1391.
50. Reeves RR. Abuse of olanzapine by substance abusers. *J Psychoactive Drugs*. 2007;39:297–299.
51. Murphy D, Bailey K, Stone M, Wirshing WC. The addictive potential of quetiapine. *Am J Psychiatry*. 2008;165:918.